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EXAMINER

KERR, KATHLEEN M

ART UNIT PAPER NUMBER

1652

18

DATE MAILED: 05/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

<b>Office Action Summary</b>	Applicati n No. 09/623,596	Applicant(s) WACHI ET AL.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication appears on th cover sheet with the c rrespondence address --

**Period f r Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 17 March 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4,6-9 and 11-27 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4,6-9 and 11-27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☒ All   b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) Paper No(s). <u>14</u> |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)               |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Application Status***

1. In response to the previous Office action, a Final rejection (Paper No. 12, mailed on June 17, 2002), Applicants filed an amendment and request for continued examination (RCE) received on March 17, 2003 (Paper NOs. 16 and 17). Said amendment amended Claims 1, 2, 3, and 9, cancelled Claim 5 and 10, and added new Claims 11-27. Thus, Claims 1-4, 6-9, and 11-27 are pending in the instant Office action and will be examined herein.

### ***Priority***

2. As previously noted, the request for the benefit of priority for the International Application No. PCT/JP99/01084 filed on March 5, 1999 and the foreign application Japan 10-55608 filed on March 6, 1998, is noted. No translation of the JP document has been filed.

### ***Drawings***

3. As previously noted, the drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

### ***Withdrawn - Objections to the Specification***

4. Previous objection to the Abstract for not completely describing the disclosed subject matter is withdrawn by virtue of Applicants' amendment.

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***Withdrawn - Claim Objections***

5. Previous objection to Claim 10 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicants' cancellation of said claim.

***Withdrawn - Claim Rejections - 35 U.S.C. § 112***

6. Previous rejection of Claims 1-3 and 5-7 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicants' amendment; a new rejection is set forth below more particularly describing several enablement problems with the instant claims. Applicant's only comments concerning the instant rejection were that the amendments obviate it; this is not the case.

7. Previous rejection of Claims 1-3 and 5-7 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of Applicants' amendment; a new rejection is set forth below more particularly describing several enablement problems with the instant claims. Applicant's only comments concerning the instant rejection were that the amendments obviate it; this is not the case.

**NEW OBJECTIONS/REJECTIONS**

***Claim Objections***

8. Claim 3 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the

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claim(s) in independent form. Claim 3 is drawn to methods using a plasmid containing PBP under the control of a temperature sensitive promoter. This does not appropriately further limit from Claim 2, which requires a temperature sensitive mutation within the sequence of the PBP gene ("because of a mutation in said PBP").

***Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-3, 6-7, and 17-27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is confusing as to the structure of the coryneform bacteria used in the methods, particularly the DNA in the bacteria. It is unclear how a penicillin binding protein (PBP) is "not produced" when the gene, or something structurally similar to the gene, is present. In other words, what has been deleted is found in the claim limitations – but the instant claims are not particular to *C. glutamicum* and the deletion of SEQ ID NO:1. The Examiner suggests the following:

- a) Write a claim drawn to deleting all or a portion of the chromosomal copy of the PBP so that this copy is inactive and transforming the cell with a functioning PBP on a plasmid. From this, write a dependent claim to a temperature sensitive plasmid.
- b) Write a claim drawn to deleting all or a portion of the chromosomal copy of the PBP so that this copy is inactive and inserting a functioning PBP under the control of a temperature sensitive replicon into the chromosome.

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10. Claims 9, 12, 14, and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 9, the phrase "derived from" is unclear. Must the claimed DNA be native to coryneform or can the DNA merely be obtained from any coryneform host? Claims 11, 13, and 15 do not need clarification because their structures are specifically defined by other claim limitations. Clarification is required for the instant claims.

11. Claims 9, 11, 13, and 15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 9, item a, the term "at" is confusing and should be deleted so that claim reads ---a DNA which comprises nucleotides 881 to 2623 of SEQ ID NO:1---. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 2 and 21 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to methods using a penicillin binding protein (PBP) gene having a temperature sensitive mutation that

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affects the activity of the PBP. While the specification describes using PBP genes under the control of temperature sensitive promoters, no mutation within the PBP gene is described that affects PBP activity only at certain temperatures.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any representative species of a mutation within the PBP gene that affects PBP activity only at certain temperatures. Therefore, Claims 2 and 21, as written, fail to satisfy the written description requirement.

13. Claims 9, 12, 14, and 16 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant rejection is specifically recited against Claim 9, item (b). Claim 9 is drawn to DNA encoding a penicillin binding protein (PBP), wherein the DNA is structurally related to SEQ ID NO:1 from nucleotides 881-2623 and wherein the DNA is native to coryneform.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function

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and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

In the specification, a single example of a PBP from coryneform that meets the structural limitations of Claim 9 is described – that is, SEQ ID NO:1 from 881-2623. No examples of other coryneform sequences are described, either PBP sequences or general coryneform sequences. The instant claims are drawn to a *subgenus* of all PBP genes within the claimed structural limitations, wherein the DNA must be from coryneform. The specification does not describe coryneform PBP sequences to the exclusion of PBP sequences from other sources. Clearly, PBP sequences from coryneform within the structural limitations are enabled by the disclosure; however, one of skill in the art would be unable to recognize other members of the claimed subgenus to the exclusion of, for example, PBP genes from *E. coli*, within the structural limitations. Thus, the claimed subgenus does not have adequate written description. The Examiner suggests the deletion of the phrase “derived from coryneform bacteria” to obviate the instant rejection.

14. Claims 1, 6, 17-20, 23, and 25-27 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using coryneform bacteria with a functioning PBP at particular temperatures for growth, does not reasonably provide enablement for methods coryneform bacteria without a functioning PBP at any temperature. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To practice such a method in the absence of a functioning PBP gene on the coryneform bacteria would require undue experimentation. Claims 2, 3, 7, 21, 22, 24 are



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specifically limited to methods using coryneform bacteria with a temperature sensitive mutation involved in the control of the activity of the PBP, wherein PBP activity is regained at certain temperatures to allow for bacteria growth.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant specification on page 37, the production of a temperature-sensitive-PBP-containing coryneform bacteria is described. It is clearly noted that a normal PBP gene is required for growth. Thus, in the absence of a functioning PBP, the coryneform cannot grow and, thus, cannot produce glutamate. No guidance or working examples of PBP<sup>-</sup> coryneform

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bacteria to be used in the claimed methods is found. The state of the prior art describes many lethal deletion mutations; SEQ ID NO:2 is described as another such example. The ability to compensate for a PBP<sup>-</sup> strain by some other means is wholly unpredictable. Thus, the instant claims are not enabled to the full extent of their scope.

15. Claims 1-3, 6-7, 18-24, and 26-27 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using coryneform bacteria with a reduced or eliminated PBP by virtue of a deletion, does not reasonably provide enablement for methods using coryneform bacteria with a reduced or eliminated PBP by virtue of a mutation other than deletion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To produce a mutated PBP with reduced activity wherein the mutation is NOT a deletion would require undue experimentation. Claims 17 and 25 are specifically limited to methods using coryneform bacteria with a deletion in the PBP gene to achieve reduced or eliminated activity.

The factors to be considered in determining whether undue experimentation is required are summarized above.

No working examples or guidance for the non-deletion mutation of SEQ ID NO:2, or structurally similar proteins, to produce a PBP with reduced penicillin binding activity is found in the specification; all mutations are via deletion. While the state of the art is replete with examples of mutated proteins having reduced activity by virtue of a point mutation, such mutants protein-specific and cannot be correlated to the instant example without extensive information about structure relatedness. The ability to produce a reduced activity, non-deletion mutant PBP,

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similar to SEQ ID NO:2 is wholly unpredictable. Thus, Claims 1-3, 6-7, 18-24, and 26-27 are not enabled to the full extent of their scope by the specification as originally filed.

16. Claims 2 and 21 are rejected under 35 U.S.C. § 112, first paragraph, enablement, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant methods are drawn to methods using PBP genes with mutations within the PBP gene itself that produces a temperature PBP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To produce such a PBP gene would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

Since no examples of temperature sensitive PBP proteins are described in the specification, no working examples are present. No guidance for the production of temperature sensitive PBPs is found in the specification. While the state of the prior art offers numerous examples of temperature sensitive proteins, these examples are protein-specific and cannot be correlated to the instant example without extensive information about structure relatedness. The ability to produce a mutant PBP, similar to SEQ ID NO:2, that functions to bind penicillin only at particular temperatures, is wholly unpredictable. Thus, Claims 2 and 21 are not enabled by the specification as originally filed.

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***Claim Rejections - 35 U.S.C. § 101***

35 U.S.C. § 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

17. Claims 8-9 and 11-12 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Claims 8 and 9, as written, do not sufficiently distinguish over cells as they naturally exist because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g. by insertion of “isolated” or “purified” as taught by page 34 of the specification. See M.P.E.P. § 2105.

***Summary of Pending Issues***

18. The following is a summary of the issues pending in the instant application:

- a) Claim 3 stands objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.
- b) Claims 1-3, 6-7, and 17-27 stand rejected under 35 U.S.C. § 112, second paragraph, for Claim 1 being wholly confusing.
- c) Claims 9, 12, 14, and 16 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “derived from”.
- d) Claims 9, 11, 13, and 15 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “at”.

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- e) Claims 2 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, written description, for using a penicillin binding protein (PBP) gene having a temperature sensitive mutation that affects the activity of the PBP.
- f) Claims 9, 12, 14, and 16 stand rejected under 35 U.S.C. § 112, first paragraph, written description, for the subgenus of DNA that is native to coryneform.
- g) Claims 1, 6, 17-20, 23, and 25-27 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, for not reasonably providing enablement for methods using coryneform bacteria without a functioning PBP at any temperature.
- h) Claims 1-3, 6-7, 18-24, and 26-27 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, for not reasonably providing enablement for methods using coryneform bacteria with a reduced or eliminated PBP by virtue of a mutation other than deletion.
- i) Claims 2 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, enablement, for methods using PBP genes with mutations within the PBP gene itself that produces a temperature PBP.
- j) Claims 8-9 and 11-12 stand rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

***Allowable Subject Matter***

19. As previously noted, Claims 8 and 9 are considered free of the prior art. The closest prior art was noted in the previous Office action as Cole *et al.* teaching a *M. tuberculosis* gene encoding a “probably penicillin binding protein”. The structural similarities between the *M. tuberculosis* gene and SEQ ID NO:1 are outside the metes and bounds of Claims 8 and 9.

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***Conclusion***

20. Claims 1-4, 6-9, and 11-27 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229.

The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK

May 26, 2003

